EXHIBIT 602.11

SECOND EDITION

HEART DISEASE

A Textbook of Cardiovascular Medicine

Edited by

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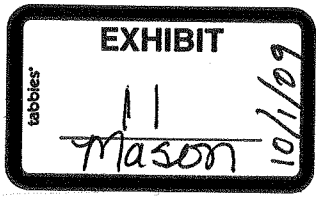

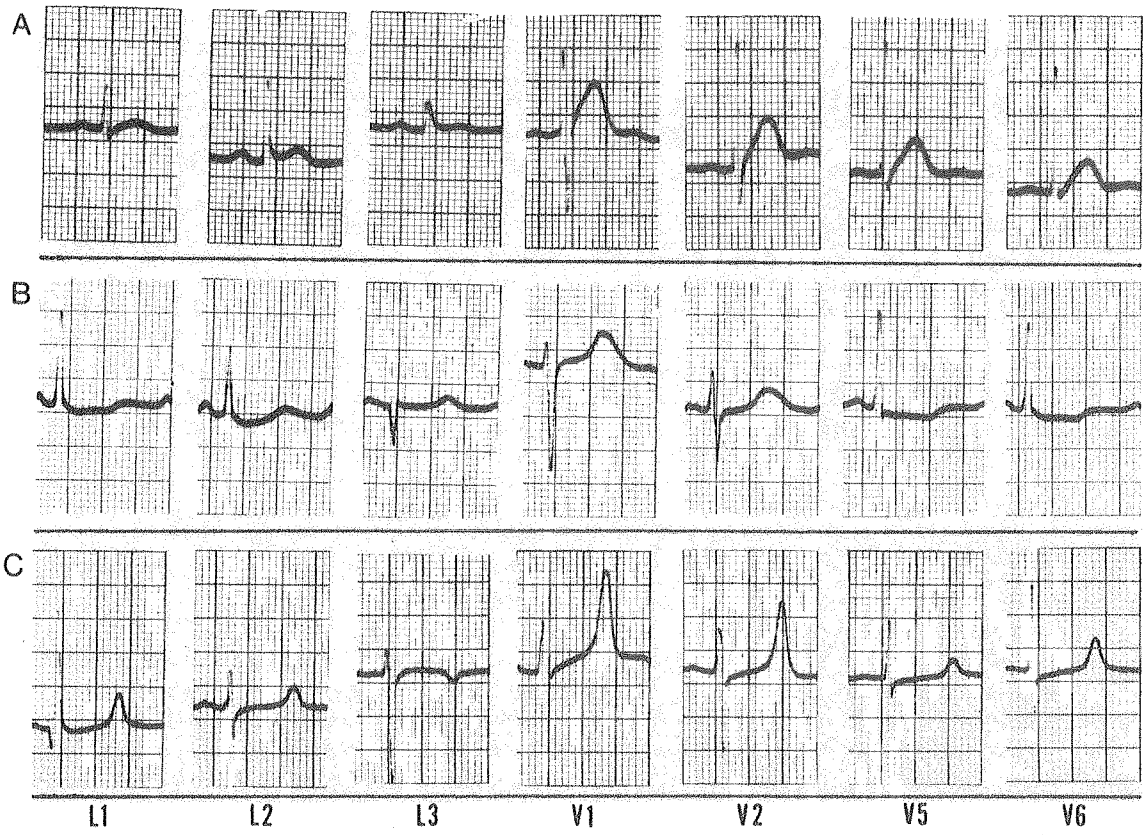

FIGURE 7–45 ECG changes of hypercalcemia, hypocalcemia, and hypocalcemia with hyperkalemia. *A*, Tracing recorded at a Ca^{++} level of 17.0 mg/dl shows short ST segment of hypercalcemia. *B*, At a Ca^{++} level of 5.9 mg/dl the Q-T interval is prolonged characteristic of hypocalcemia. *C*, Tracing recorded at a K^{+} level of 6.2 mEq/liter, Ca^{++} of 5.3 mg/dl, and phosphorus of 12.2 mg/dl. The prolonged Q-T interval and the tented T wave reflect hypocalcemia and hyperkalemia seen in chronic renal disease. (Fisch, C.: Electrolytes and the heart. *In* Hurst, J. W. (ed.): The Heart. New York, McGraw-Hill Book Co., 1982, p. 1599.)

EFFECTS OF DRUGS ON THE ECG

DIGITALIS (See also p. 523)

The cardiac glycosides differ little with regard to their effect on the ECG. Alterations of the ST segment and T wave are the earliest recognizable changes due to digitalis. The T-wave amplitude is lowered, and the ST segment is depressed and shortened, with occasional appearance of a prominent U wave.[252] While the "characteristic" digitalis-induced ST segment is described as sagging, it is often difficult if not impossible to differentiate it from ST-segment depression of other causes. When the ST segment is also shortened, digitalis is the likely cause of the depression. ST-segment displacement due to digitalis may be greatly exaggerated by myocardial disease, tachycardia, and high-amplitude QRS complexes. Rarely, digitalis causes symmetrical inversion of the T wave similar to that in pericarditis and ischemia, but there is usually associated shortening of the Q-T interval. A peaked, "tented" T wave, probably due to concomitant hyperkalemia, can also be present.

Digitalis has no significant effect on depolarization of the atrium or ventricle. Consequently, prolongation of intraatrial and intraventricular conduction is rare.[253]

Classification of Digitalis-Induced Arrhythmias. Digitalis has been known to induce nearly every known arrhythmia, and a comprehensive discussion of the subject is beyond the scope of this review.[254–256] The following general classification, based on the electrophysiological effects of the cardiac glycoside and less so on the ECG morphology or site of origin of the arrhythmia, encompasses most of the digitalis-induced arrhythmias. The classification is enlarged upon in Table 7–6 and is discussed in terms of clinical relevance below.

1. Ectopic rhythms due to enhanced automaticity or reentry or both and, perhaps, to delayed diastolic afterdepolarizations (p. 620) (Fi 46): atrial tachycardia with block (see Fig. 21–13, p. 701), atrial lation and flutter, nonparoxysmal junctional tachycardia, (Fig. 2 p. 705), ventricular premature contractions, ventricular tachyc (Fig. 7–46), ventricular flutter and fibrillation, multiple ectopic rhyt bidirectional ventricular tachycardia (Fig. 7–47), or accelerate cape.
2. Depression of pacemaker: Sinoatrial node arrest (p. 691).
3. Depression of conduction: SA block, AV block, exit block, ciprocation.
4. AV dissociation: Suppression of the dominant pacemaker passive escape of the lower junctional focus or inappropriate acc ation of a subsidiary pacemaker, or, rarely, dissociation within th junction (double junctional tachycardia).

Therapeutic and Toxic Effects. Appearance of ectopic rhythr the course of digitalis administration is nearly always a sign of t ty. On the other hand, depression of AV conduction may at time a desirable therapeutic endpoint. Acknowledging that some degr overlap is unavoidable and that the clinical significance of an arr mia may differ depending on the setting, we can divide the effec digitalis on the ECG into three general groups—therapeutic, e sive and/or toxic, and unequivocally toxic.

Clinically acceptable effects of digitalis include some prolong of the P-R interval; slowing of the ventricular response in atrial f and fibrillation: and in atrial fibrillation, the appearance of isolate junctional escape impulses. Conversion of atrial arrhythmias to rhythm, either directly or indirectly, is another desirable effect o drug.

Excessive or toxic effects, or both, are heralded by the appear of atrial tachycardia with block, nonparoxysmal junctional tachyc (Fig. 7–48), AV dissociation, second- and third-degree AV block

TABLE 7–6 CARDIAC ARRHYTHMIAS DUE TO DIGITALIS (10 STUDIES, 661 PATIENTS)

	No. of Series	No. of Arrhythmias	
Ventricular Arrhythmias		470 (71%)	
Ventricular premature contractions			420
Bigeminy	9		150
Multifocal	4		121
Not specified	4		79
Other (frequent, unifocal, occasional, etc.)	3		70
Ventricular tachycardia	7		50
AV Block		194 (29%)	
First-degree	7		87
Second-degree	10		58
Wenckebach	3		4
Third-degree	6		37
Unspecified	2		12
Atrial Arrhythmias		177 (26%)	
Atrial fibrillation	9		80
with slow rate	2		21
PAT with block	7		59
Atrial premature beats	4		27
Atrial flutter	4		11
Sinoatrial Node Arrhythmias		85 (13%)	
Sinus tachycardia	3		29
Sinus bradycardia	4		27
with nodal escape	1		11
Sinus arrest	2		11
SA block	3		7
Wandering pacemaker	3		11
AV Dissociation	4	65 (9.8%)	
AV Nodal Arryhthmias		47 (7%)	
Nodal tachycardia	4		32
Nodal rhythm	2		11
Nodal premature beats	1		4

From Knoebel, S.B., and Fisch, C.: Recognition and therapy of digitalis toxicity. Progr. Cardiovasc. Dis. *13*:71, 1970.

paroxysmal junctional tachycardia is generally perfectly regular and the diagnosis usually simple. Recognition becomes more difficult in the presence of exit block.[266] A high degree of exit block may suggest a slow junctional rhythm or AV block. If the exit block is Mobitz (type II), with 3:2 exit block, a bigeminal rhythm

longer cycles exact multiples of shorter cycles. If the exit block is Wenckebach (type I), the gradually shortening R-R interval and lack of the expected relationship of the long pause to the shorter cycles (i.e., the pause is not a multiple

not be differentiated from atrial fibrillation. Occasionally, this arrhythmia is masked and becomes evident with slowing of the dominant rhythm; it may appear as nonparoxysmal junctional tachycardia or as a single accel-

with aberrant intraventricular conduction from ventricular tachycardia may be difficult if not impossible. A rapid heart rate, a bizarre QRS complex, and AV dissociation are common to both arrhythmias. In the presence of

ciated with fusion and capture complexes.[267]

VENTRICULAR ARRHYTHMIAS. Ventricular premature contractions (VPC) are the most common manifestation of digitalis toxicity but, at the same time, are the

morphological features of the QRS complex helps entiate VPC due to digitalis from those of oth The exception is ventricular bigeminy, with acc pling but varying morphology—a criterion that tive of digitalis toxicity.

duced VPC are also applicable to ventricular

Ventricular tachycardia with exit block

bidirectional ventricular tachycardia

suggest digitalis intoxication. A bidirectional

ventricular tachycardia originates in the divisions o bundle branch, the QRS complex may be normal tion, and the diagnosis rests on the presence of ial capture and fusion complexes. Studies in ani

Digitalis-induced ventricular fibrillation is se corded in man. It is rarely, if ever, the initial man of digitalis toxicity but is usually preceded by o talis-induced arrhythmias.

This is particularly the case when parasyst accompanied by other arrhythmias known to be digitalis intoxication.

The presence of diverse ectopic rhythms, either conduction.[235]

AV DISSOCIATION (see also p. 735). AV tion appearing in the course of digitalis administ strongly indicative of digitalis overdosage or